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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/820,200	04/07/2004	Henrik Bisgard-Frantzen	5835.210-US	7464

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NOVOZYMES NORTH AMERICA, INC.  
500 FIFTH AVENUE  
SUITE 1600  
NEW YORK, NY 10110

EXAMINER

MONSHIPOURI, MARYAM

ART UNIT PAPER NUMBER

1653

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Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 10/820,200	<b>Applicant(s)</b> BISGARD-FRANTZEN ET AL.	
	<b>Examiner</b> Maryam Monshipouri	<b>Art Unit</b> 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is FINAL.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 31-48 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 31-48 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>filed 4/7/2004</u> . | 6) <input type="checkbox"/> Other: ____.  |

### **DETAILED ACTION**

Claims 1-30 are canceled. Claims 31-48 are under examination on the merits.

#### ***Priority***

It is noted that applicant claims foreign priority to Danish patent PA 1999 01617, certified copies of which are present in the parent Application No. 09/710,339. It is requested that applicant resubmits a copy of said certified patent in response to this office, action for clarity of record.

#### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear how claim 32 variant, which requires a mutation in amino acid 153 of SEQ ID NO:2 is within the scope of claim 31 which only allows mutations in regions 98-110 and 161-167 of SEQ ID NO:2, appropriate clarification is required.

Claims 31-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "each region or position corresponds to a region position of the amino acid sequence of the parent ..." in claim 31 (and its dependent claims 32-48) is unclear. Also it is unclear as to why the term "region" in line

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2 of claim 31 starts with the capital letter but in line 7 does not. Appropriate clarification is required.

Claim 37 recites the limitation "brewing composition of claim 41". There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for variants of SEQ ID NO:2 as recited in claim 31, having at least 97% identity to SEQ ID NO:2 with amylase activity, does not reasonably provide enablement for variants of SEQ ID NO:2 as recited in claim 31 having at least 70%-95% identity to said amino acids sequence while retaining fungamyl-like alpha-amylase activity.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2n 1400 (Fed. Cir. 1988) are: 1) the quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breadth of the claims.

In claim 31, applicant is claiming amylase variants that allow merely 4 % amino acid residue change in entire amino acids sequence of SEQ ID NO:2 composed of 498 residues in total.  $13$  (corresponding to residues 98-110) +  $7$  (corresponding to residues 161-167) =  $20$ , which when divided by total amino acids of SEQ ID NO:2, 498, results in

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approximately 4% variation). However, in dependent claims 42-46 many extra amino acid residues must be mutated to make up for structural requirements of 70-95% homologs of SEQ ID NO:2.

The specification fails to teach which amino acid residues beyond those in regions 98-110 and 161-167 of SEQ ID NO:2 must be retained in the claimed homologs of SEQ ID NO:2 such that said homologs retain alpha-amylase activity. No examples of such residues are provided either. Current state of the art indicates that once three or more residues beyond those recited in regions 98-110 and regions 161-167 are deleted, substituted etc. claimed homologs may not necessarily retain the appropriate three dimensional structure in order to retain alpha-amylase activity.

Therefore to lack of sufficient guidance and examples provided in the specification and due to unpredictability of prior art as to which residues in claimed 70% or higher homologs of fungamyl like alpha-amylases must be kept intact such that claimed homologs retain the appropriate three dimensional structure for retaining amylase function one of skill in the art has to go through the burden of undue experimentation in order to prepare those alpha-amylase homologs that are within the scope of this invention and as such the claims are not enabled.

Claims 42-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 42-46 are directed to a **genus** of

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alpha-amylase homologs that have been inadequately described in the specification.

As stated above, In claim 31, applicant is claiming amylase variants that allow merely 4 % amino acid residue change in entire amino acid sequence of SEQ ID NO:2 composed of 498 residues in total. **13** (corresponding to region 98-110) + **7** (corresponding to residues 161-167) = **20**, which when divided by total amino acids of SEQ ID NO:2, 498, results in approximately 4 % variation). However, in dependent claims 42-46 many extra amino acid residues must be mutated to make up for structural requirements of 70-95% homologs of SEQ ID NO:2.

The specification does not contain any disclosure of the structure of all alpha-amylase homologs sequences that are 70-95% identical to SEQ ID NO:2 beyond the 20 amino acids indicated above. Applicant is well aware that for a polypeptide to have any activity its three dimensional structure must remain intact or close enough to the wild-type polypeptide. Therefore, some additional information beyond those provided for regions 161-167 and 98-110 is needed in order to describe the genus of homologs as broadly claimed. Currently, the genus of polypeptides that comprise these above polypeptide molecules is a large variable genus with the potentiality of encoding many different proteins. Therefore, many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a **single species** (SEQ ID NO:2 with allowed mutations in regions 98-110 and 161-167) of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one

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skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised interim guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at [www.uspto.gov](http://www.uspto.gov).

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 31-48 are provisionally rejected under the judicially created doctrine of double patenting over claims 31-33, 39-43, 50-62 of copending Application No.

09/710,339. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant

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application are claiming common subject matter, as follows: the scope of the claims recited in the parent application 09/710,339 embrace the scope of claims in instant application.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application.

***Claim Rejections - 35 USC § 103***

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. Claims 31-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Christianson (U.S. Patent No. 6,136,553, 11/2000, cited in the IDS) in view of Matsuura et al. (J. Biochem., 95, 697-702, 1984, cited in the IDS) further in view of Svendsen et al. (WO 96/23874, 8/1996, cited in the IDS). Christianson teaches and claims a method of identifying amino acid sites in a target protein which affect the stability, pH sensitivity of the target protein comprising (1) inputting the three dimensional coordinates of said target protein into a computer, (2) generating a probe-accessible surface of said target protein (3) identifying the amino acids which make up the boundaries of internal cavities which affect the stability of the protein, (4) mutating at

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least one of the sites to create a mutant target protein (5) expressing and isolating the mutant target protein and testing the mutant target protein for stability (see claims 1-2 ). Christianson does not use alpha amylase, set forth as SEQ ID NO:2 of this invention, as target protein.

Matsuura teaches the complete amino acid sequence of *Aspergillus oryzae*, matching SEQ ID NO:2 of this invention completely, as well as its three dimensional crystal structure.

At the time the invention was made it would have been obvious to one of ordinary skill in the art to start with the method of Christianson and replace its target protein with alpha amylase of Matsuura in order to prepare variants with structural and functional properties as taught by Svendsen. This is because Matsuura's enzyme has a crystal structure that is known and Svendsen's recommended regions (loops of interest) could be easily used as a guide in order to find equivalent regions within the structure of instant alpha amylase which can be identified according to Christianson, in order to result in a more stable, heat resistant or acid resistant amylase variants.

For example, Svendsen in page 1 teaches that almost all alpha amylases have a few conserved regions with approximately the same length and spacing. One of these regions resembles calcium binding site and the others are thought to be necessary for active center and/or binding of the substrate. According to Svendsen hybrid amylases may be prepared wherein certain loop regions of termamyl amylase may be replaced with equivalent loop regions (identified by sequence and crystal structure comparisons) of amylase from *Aspergillus* source such as SEQ ID NO:2 of this invention (see pages

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8-14). In page 36 Svendsen also teaches that termamyl alpha amylase structure contains a number of unique internal holes, which may contain water and a number of crevices. Svendsen further indicates that for example, in order to increase the thermostability of the amylase it may be desirable to reduce the number of holes and crevices by introducing bulkier residues, in the vicinity or surroundings of the hole (see pages 36-40). Svendsen then teaches a series of variants including S151 (see page 38), V259, F284 (see page 39) and L427, V481 (see page 40) which could be good candidates for mutation resulting in more thermostable amylase variants.

Svendsen also indicates that (see page 57) that its amylase variants may be useful in production of edible products such as sweeteners and ethanol from starch implying preparing maltose syrups, dough and brewing compositions comprising amylase variants. In addition immobilized preparation of enzymes such as glucose isomerase for the preparation of fructose syrup is also suggested by Svendsen.

One of ordinary skill in the art is motivated to prepare SEQ ID NO:2 variants in which residues equivalent to, for example, L61, Y62, F67, K106, G145, I212, S151, V259, F284 and L427 of Svendsen, located in regions equivalent to region 98-110, 161-167 and region 468-475 of SEQ ID NO:2, identified according to Christianson, are mutated because mutating such equivalent residues in instant amylase will result in products that can be used in either free or immobilized form (prepared by methods similar to those applied to glucose isomerase, see page 57 of Svendsen) in fermentation, sweetener preparation and baking etc. tolerating higher temperatures thereby rendering amylase variants more useful and desirable for commercial

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applications. Such SEQ ID NO:2 mutants will inherently have at least 70% identity to SEQ ID NO:2 of this invention depending on how many amino acids are simultaneously deleted, substituted, inserted etc.

Further, one of ordinary skill in the art has a reasonable expectation of success in mutating amylase of this invention at equivalent sites and loops recommended by Svendsen identified by methods of Christianson, because the crystal structure of SEQ ID NO:2 of this invention is known, the instructions as to which loops should be targeted for what properties, methods of identifying amino acid sites (such as substrate binding loop(s), stability enhancement loops etc.) in target proteins (including amylases), their homologs and/or equivalents as well as methods of preparing mutant amylase products using site directed mutagenesis techniques are well established in the prior art, rendering claims 31-48 obvious.


**No claims are allowed.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maryam Monshipouri whose telephone number is (571) 272-0932. The examiner can normally be reached on 7:00 a.m to 4:30 p.m. except for alternate Mondays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Weber Jon P. can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306 or (571)273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

  
Maryam Monshipouri Ph.D.

Primary Examiner

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